UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/091,357	03/01/2002	Sivaram Pillarisetti	18631-0141 (45115-268551)	7257

26158 7590 03/10/2006

WOMBLE CARLYLE SANDRIDGE & RICE, PLLC
ATTN: PATENT DOCKETING 32ND FLOOR
P.O. BOX 7037
ATLANTA, GA 30357-0037

EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/091,357	PILLARISETTI, SIVARAM	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5 and 17-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5 and 17-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/15/05 has been entered.

2. Claims 1, 3-5 and 17-24 are pending.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 5 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 5 is seen to be improper, since it is drawn to a compound that is a chemical molecule. In chemistry, compounds requisitely contain two or more elements. The instant claim 5 fails to provide two or more elements. The recitation of a single chemical element or chemical molecule renders claim 5 indefinite.

B. The "stabilizes production of HSPG" recited in claim 19 has no antecedent basis in base claim 1. Base claim 1 only recites an increase or decrease in the amount of the HSPG.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 3-5 and 17-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting a compound that affect cell proliferation comprising adding a compound comprising unknown cellular proliferative activity to a first cell culture, measuring the amount of HSPG in the first cell culture; and comparing the amount of HSPG in the first cell culture to the amount of HSPG in a second cell culture not treated with the compound, wherein an increase or decrease in the amount of the HSPG in the first cell culture as compared to the amount to the HSPG in the second cell culture indicates that the compound affects cell proliferation , does not reasonably provide **enablement** for a method

for detecting a compound that affect cell proliferation comprising adding the compound comprising unknown cellular prolifeative activity to a first cell culture; measuring the amount of "any HSPG" in the first cell culture, and comparing the amount of HSPG in the first cell culture to the amount of any HSPG in a second cell culture not treated with the compound in claim 1, wherein the HSPG is syndecan or glypican in claims 3 and 23-24. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification fails to teach how to measure the amount of either syndecan or glypican in cell culture. Neither does the specification teach how to discriminate between prelecan, syndecan or glypican when measuring the amount of HSPGs.

Further at issue the claimed molecule of claim 5, the specification does not provide guidance the skilled artisan as to what molecules to be screened. While the dictionary provides a meaning for the word molecule as the smallest particle of a substance that retains the chemical and physical properties of the substance and is composed of two or more atoms; a group of like or different atoms held together by chemical forces. However, the specification fails to provide such chemical and physical properties of the claimed molecule.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Applicant's arguments, filed 12/15/05, have been fully considered, but have not been found persuasive.

Applicant maintains that one skilled in the art can without undue experimentation measure the amount of HSPG without a need for antibodies. Applicant asserts that the specification discloses the amount of HSPG in a cell can at least be measured by for example a procedure involving (^{35}S) sulfate radiolabel and DEAE-cellulose chromatography.

However, the specification discloses that such a method would measure the total PGs including the perlecan (i.e., not specific for any HSPGs). However, claim 3 recites that the HSPG is perlecan, syndecan or glypican. It is still unclear how to measure the amount of syndecan or glypican in the first cell culture.

Applicant further asserts that the skilled artisan would be able to measure perlecan, syndecan or glypican or discriminate between perlecan, syndecan, or glypican at least by measuring the amount of their respective ribonucleic acids such as for example, their respective mRNA.

However, claim 1(b) recites measuring the amount of a HSPG in the first cell culture, not the amount of a HSPG in said cells. Since measuring mRNA expression requires isolating the mRNA from said cells. No mRNA is secreted by the cells to the cell culture for one skilled in the art to perform mRNA expression profile of the PGs.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 5, 17 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Paka *et al* (abstract Nov. 2, 1999).

Paka *et al* teach a method determine whether the anti-proliferative effect of apoE is due to increased HS production. Paka *et al* teach that apoE stimulates endothelia production of heaparan sulfate (HS) enriched in heparin-like sequences. Further, Paka *et al* teach that given that heparin and HS are potent inhibitors of smooth muscle cell (SMS) proliferation, they determined whether the anti-proliferative effect of apoE is due to increased HS production. Paka *et al* teach that by adding apoE to confluent SMC, it increased $^{35}SO_4$ incorporation into cells by 24% and media by 36%. Paka *et al* teach that the increase in the medium was exclusively due to an increase in HS (2.1 fold) and apoE did not alter chondroitin and dermatan sulfate proteoglycan (PG). While adding apoE to proliferating SMC, it inhibited bFGF/EGF stimulated (^{3}H)thymidine incororporation into DNA by 50%, despite decreasing cell number, apoE increased the ratio of $^{35}SO_4$ to (^{3}H)thymidine) from 2-3.5 suggesting increased HS per cell. Finally, Paka *et al* teach that analysis of the conditioned medium from apoE stimulated cells revealed that the HSPG increase was in perlecan and apoE also stimulated perlecan mRNA expression by >2 fold. Paka *et al* concluded that the ability of apoE isoforms to inhibit SMC proliferation correlated with their ability to stimulate perlecan production and E2 and E4 (compounds comprising unknown cellular proliferative activity) were less effective in stimulating perlecan production (see the entire abstract in particular).

Claim 5 is included because apoE2, apoE3 and apoE4 are considered to be a molecule.

Claim 19 is included because apoE2 and apoE4 did not significantly increase perlecan HSPGs or inhibit cell proliferation (stabilizes production).

The reference teachings anticipate the claimed invention.

Applicant's arguments, filed 12/15/05, have been fully considered, but have not been found persuasive.

Applicant argues that ApoE according to Paka et al, is a compound having known cellular proliferative activity.

While Paka et al teaches that ApoE comprises known cellular proliferative activity, Paka et al determine which ApoE isoform such as E2 and E4 (compounds comprising unknown cellular proliferative activity) effects SMC proliferation. Until the time Paka's *et al* abstract, it was not known which ApoE isoform effects the SMC proliferation. Paka *et al* concluded that the ability of apoE isoforms to inhibit SMC proliferation correlated with their ability to stimulate perlecan production and E2 and E4 were less effective in stimulating perlecan.

Applicant argues that Paka does not detect a compound that affects cell proliferation either by adding a compound having unknown cell proliferative activity or by measuring and comparing the amount of HSPG to indicate cell proliferation.

Contrary to Applicant argument, Paka *et al* detect the a compound that affects cell proliferation by adding a compound having unknown cell proliferative activity such as E2, E3 and E4 isoforms of ApoE and measuring and comparing the compound of HSPG using $^{35}SO4$ incorporation into media (measuring total PGs in the media), the comparing component of the claim is an inherent step in the Paka et al method.

9. Claims 1, 3-5, 17, 19-20 and 22-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Paka *et al* (JBC, Dec. 1999, IDS Ref. No. 22).

Paka *et al* studies the effects of ApoE isoforms (E2, E3 and E4) and anti-perlecan antibody (compounds comprising unknown cellular proliferative activity) on perlecan production and proliferation (see Fig. 6 and 7) of subconfluent SMCs using [^{3}H]Tymidine incorporation and compared to control (medium alone). Paka et al teaches that ApoE3, the most common isoform of apoE, showed maximum stimulation on perlecan production and inhibition on cell proliferation (45%). ApoE2 and apoE4 did not significantly increase perlecan HSPGs or inhibit cell proliferation (see page 36406 under *Effects of ApoE Isoforms* in particular). Paka et al teach that perlecan antibody did not affect cell growth under control conditions in rat SMS, however in human SMC, the perlecan antibody stimulated SMS proliferation by 30-35% (see abstract, Figs 7 and page 36406 under *The Antiproliferative Effect of ApoE requires Perlecan* in particular). Paka et al also teaches that a method of determining of perlecan protein in SMCs media, wherein PGs are isolated from SMC medium and purified by DEAE-cellulose chromatograph. Pruified PGs are immunoprecipitated with an anti-perlecan antibody, and analyzed by 5% SDS-PAGE. Then identify perlecan by autoradiograph (see page 36404, under *Determination of Perlecan protein and mRNA*, and Figs 5 in particular). Further, Paka et al teach a method of assessing medium PG levels using [^{35}S]sulfate and DEAE-cellulose chromatography (see page 36404, under *Metabolic Labeling* and *DEAE cellulose Chromatography of PGs* in particular). Paka et al conclude that the antiproliferative HSPG in SMC medium is perlecan. Paka et al teach that the

cells were grown in MEM containing 10% FBS (see page 36404, 1st col., lines 2-3, and fig 1 description in particular). Lastly, Paka et al teach that cell surface syndecan may be used to determine HSPGs mediating antiproliferative effect of apoE, since it is a signaling receptor and the alterations in the phosphorylation state of syndecan may affect cell growth (see page 36408, 1st col,, 1st paragraph in particular).

Claim 5 is included because apoE isoforms and anti-perlecan antibody are considered to be a molecule.

Claim 19 is included because apoE2 and apoE4 did not significantly increase perlecan HSPGs or inhibit cell proliferation (stabilizes production). The antibodies in the rat SMC did not affect cell growth.

The reference teachings anticipate the claimed invention.

Applicant's arguments, filed 12/15/05, have been fully considered, but have not been found persuasive.

Applicant submits that Paka does not teach or suggest detecting compound that affects cell proliferation by adding a compound having unknown cell proliferative activity nor by measuring and comparing the amount of HSPG to indicate cell proliferation.

Contrary to applicant assertion Paka teaches methods of detecting compounds that affect cell proliferation by adding apoE isoforms (apoE2, apoE3, and apoE4) or anti-perlecan antibodies (having unknown cell proliferative activity) by measuring and comparing the amount of HSPG including perlecan, to indicate cell proliferation.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1, 3-5, 17, 19 and 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paka *et al* (Dec, 1999) in view of Lee (2000).

Paka *et al* teach a method determine whether the anti-proliferative effect of apoE is due to increased HS production. Paka *et al* teach that apoE stimulates endothelia production of heaparan sulfate (HS) enriched in heparin-like sequences. Further, Paka *et al* teach that given that heparin and HS are potent inhibitors of smooth muscle cell (SMS) proliferation, they determined whether the anti-proliferative effect of apoE is due to increased HS production. Paka *et al* teach that by adding apoE to confluent SMC, it increased $^{35}SO_4$ incorporation into cells by 24% and media by 36%. Paka *et al* teach that the increase in the medium was exclusively due to an increase in HS (2.1 fold) and apoE did not alter chondroitin and dermatan sulfate proteoglycan (PG). While adding apoE to proliferating SMC, it inhibited bFGF/EGF stimulated (^{3}H)thymidine incororporation into DNA by 50%, despite decreasing cell number, apoE increased the ratio of $^{35}SO_4$ to (^{3}H)thymidine) from 2-3.5 suggesting increased HS per cell. Finally, Paka *et al* teach that analysis of the conditioned medium from apoE stimulated cells revealed that the HSPG increase was in perlecan and apoE also stimulated perlecan mRNA expression by >2 fold. Paka *et al* concluded that the ability of apoE isoforms to inhibit SMC proliferation correlated with their ability to stimulate perlecan production and E2 and E4 were less effective in stimulating perlecan (see the entire abstract in particular). Lastly, Paka et al teach that cell surface syndecan may be used to determine HSPGs mediating antiproliferative effect of apoE, since it is a signaling receptor and the alterations in the phosphorylation state of syndecan may affect cell growth (see page 36408, 1st col,, 1st paragraph in particular).

The claimed invention differs from the reference teachings only by the recitation of compound comprising unknown cellular proliferative activity in claims 1and 22-24.

Lee teaches that in order to develop an effective treatment for restenosis, it is important that efforts be directed to identifying endothelial compounds, other than HSPG, that regulate the vascular response to injury, other than HSPG, that regulate the vascular response to injury. These compounds may be more potent than HSPG in inhibiting restenosis, or co-administration of these compounds with heparin may prove an effective therapy (see page 177, under Proposal in particular). Lee teaches that extensive research has been devoted to identify endothelial compounds that regulate the vascular response to injury, with the hope that these compounds will serve as therapies for restenosis. Lee also teaches that a multitude of agents have been discovered that inhibit SMC proliferation (see specific Aims in particular). Lee teaches that the goal is to identify potential therapies for vascular disease (see page 175, 1st col., lines 2-3 in particular). Lee teaches that HSPGs are another endothelial-derived product known to have antipoliferative properties. Further, the endothelium produces a variety of compounds that regulate normal vascular function. These compounds are especially important in controlling vascular repair after injury, and their loss can hasten obstructive vascular diseases or lead to rapid reocclussion of the artery after interventional procedures. Also, Lee teaches methods of identification of the endothelial compounds that regulates the vascular response to injury in a

crucial step toward elucidating the cellular and molecular mechanisms underlying restenosis as well as toward developing therapies for restenosis (see scientific abstract in particular). Finally, Lee suggests to determine whether other dominant factors besides HSPG and NO contribute to the ability of tissue engineered endothelial cells to regulate smooth muscle cell proliferation. Lee suggested the test protamine and L-NAME inhibitory properties of the engineered cells.

Claim 5 is included because compounds are considered to be a molecule.

Claim 19 is included because ApoE did not alter (stabilizes production) chondroitin/dermatan sulfate proteoglycan (PG).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antiproliferative ApoE compound taught by Paka with the compounds taught by Lee in a method for detecting a compound that affects cell proliferation taught by Paka *et al*.

Since factors besides HSPG and NO contribute to the ability of tissue engineered endothelial cells to regulate smooth muscle cell proliferation, one of ordinary skill in the art at the time the invention was made would have been motivated to do so to identify compounds than are more potent than HSPG in inhibiting restenosis or co-administration of these compounds with heparin may prove an effective therapy as taught by Lee (page 177, under Proposal).

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

12. Claims 1, 3 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paka *et al* (Dec. 1999) in view of Lee (2000) and U.S. Pat. No. 6,306,613.

The teachings of Paka *et al* (Nov. 1999) and Lee article have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation that the HSPG is glypican in claims 3 and 24.

The `613 patent teaches that K-glypican is part of a growing family of cell surface heparin sulfate proteoglycans (HSPGs) that play a role in regulating cellular proliferation, differentiation, and migration. The core polypeptide of the HSPGs is typically sulfated and some of these HSPGs have been shown to interact with the leaderless protein FGF-2, which may even facilitate FGF-2 binding with its receptor (see col. 15, lines 19-25 in particular)

Given that glypican plays a role in regulating cellular proliferation, it would have been obvious to one of ordinary skill in the art at the time the invention was made to measure the amount of

glypican as taught by the `613 patent in determining cell proliferation method as taught by Paka et al (Nov. & Dec. 1999).

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because glypican plays a role in regulating cellular proliferation as taught by the `613 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. Claims 1, 3-4 and 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paka *et al* (abstract Nov. 2, 1999) in view of Paka *et al* (JBC, Dec. 1999, IDS Ref. No. 22).

The teachings of Paka *et al* (Nov. 1999) have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation that the HSPG is perlecan or syndecan in claims 3-4 and 22-23.

Paka et al (Dec. 1999) teach that demonstration of requirement for cell surface HSPGs in mediating the antiproliferative effect of apoE is difficult as agents that interfere with cell surface HSPGs, such as heparinase, heparin and chlorate, independently inhibit cell proliferation. Paka et al (Dec. 1999) further teach that cell surface syndecan is beginning to be recognized as a signaling receptor and that alterations in the phosphorylation state of syndecan may affect cell growth (see page 36407, 2nd col., last paragraph and 36408, 1st col,, 1st paragraph in particular). Paka et al also teaches a method of determining of perlecan protein in SMCs media, wherein PGs are isolated from SMC medium and purified by DEAE-cellulose chromatograph. Pruified PGs are immunoprecipitated with an anti-perlecan antibody, and analyzed by 5% SDS-PAGE. Then identify perlecan by autoradiograph (see page 36404, under *Determination of Perlecan protein and mRNA*, and Figs 5 in particular)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to measure the amount of perlecan or syndecan in cell culture as taught by Paka et al (Dec. 1999) in a method of detecting compounds that affect cell proliferation as taught by both Paka (Nov. 1999).

Given the difficulty of measuring cell surface HSPGs in mediating the antiproliferative effect of apoE (including it's isoforms), due to the presence of interfering agents with cell surface HSPGs, such as heparinase, heparin and chlorate, independently inhibit cell proliferation, one of ordinary skill in the art at the time the invention was made would have been motivated to measure the amount of cell surface perlecan or syndecan because cell surface syndecan is beginning to be

recognized as a signaling receptor and that alterations in the phosphorylation state of syndecan may affect cell growth. Further the method of measuring perlecan would result in a single band with a molecular mass slightly higher than 550 kDa as taught by Paka *et al* (Dec. 1999).

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 12/15/05, have been fully considered, but have not been found persuasive.

Applicant argues that that not only does Paka et al (Dec, 1999) lack suggestion or motivation to modify its teaching to measure the amount of HSPG instead of cells or [3H]thymidine incorporation, the reference appears to teach away from such a modification. Applicant points that "apoE increased HSPG production in endothelial cells." yet "apoE did not inhibit proliferation of endothelial cells. Further, "in certain cell types… blocking perlecan production via antisense DNA inhibited cell growth". In addition, "although in vitro all isolated HSPGs are effective inhibitors of SMC proliferation, the identity of the antiproliferative HSPGs in vivo is not known. Cell surface HSPGs are required for the mitogenic activity of several growth factors… and thus are unlikely to inhibit cell growth."

A prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). General skepticism of those in the art -- not amounting to teaching away -- is also "relevant and persuasive evidence" of nonobviousness. *Gillette Co. v. S.C. Johnson & Son,* Inc., 919 F.2d 720, 726, 16 USPQ2d 1923, 1929 (Fed. Cir. 1990). In effect, "teaching away" is a more pointed and probative form of skepticism expressed in the prior art. In any case, the presence of either of these indicia gives insight into the question of obviousness.

Here in contrast to applicant's assertions of teaching away by the prior art because the references indicate a successful method of detecting a compound that affects cell proliferation in cell culture; there is no discouragement nor skepticism in the prior art for the modification, particularly in light of the prior art teachings that factors that increase perlecan inhibit cell growth, whereas those that decrease perlecan stimulate cell growth (see page 36408 last sentence in particular).

Applicant argues that Paka et al (Nov. 1999) does not provide suggestion or motivation to modify its teaching by measuring the amount of HSPG instead of [^{3}H]thymidine incorporation.

However, Paka et al abstract provided teachings that the total PGs are measured in the medium using $^{35}SO_4$, yet Applicant referring to thymidine incorporation in the DNA of the cell.

Applicant further argues that Paka et al abstract teaches away from such a modification. Applicant points that Paka et al abstract states "we recently showed that apoE stimulates endothelial cell production of heparin sulfate (HS), yet despite such a stimulation "apoE did not inhibit proliferation of endothelia cells"

In contrast to Applicant's assertion of teaching away by the prior art of Paka et al abstract, the abstract indicate a successful method of detecting a compound that affects cell proliferation in cell culture, there is no discouragement nor skepticism in the prior art for the modification, particularly in light of the prior art teachings that other growth modulator also regulate perlecan expression through the same pathway in the regulation of SMC growth (see last sentence in particular).

14. Claims 1, 3 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paka *et al* (abstract Nov. 2, 1999) or Paka et al (Dec. 1999, IDS Ref. No. 22) in view of U.S. Pat. No. 6,306,613.

The teachings of Paka *et al* (Nov. 1999) and Paka et al (Dec. 1999) have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of glypican in claims 3 and 24.

The `613 patent teaches that K-glypican is part of a growing family of cell surface heparin sulfate proteoglycans (HSPGs) that play a role in regulating cellular proliferation, differentiation, and migration. The core polypeptide of the HSPGs is typically sulfated and some of these HSPGs have been shown to interact with the leaderless protein FGF-2, which may even facilitate FGF-2 binding with its receptor (see col. 15, lines 19-25 in particular)

Given that glypican plays a role in regulating cellular proliferation, it would have been obvious to one of ordinary skill in the art at the time the invention was made to measure the amount of glypican as taught by the `613 patent in determining cell proliferation method as taught by Paka et al (Nov. & Dec. 1999).

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because glypican plays a role in regulating cellular proliferation as taught by the `613 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at

the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 12/15/05, have been fully considered, but have not been found persuasive.

Applicant submits that nowhere in the `613 patent discloses or suggests use of HSPG, or specifically glypican, in a method for detecting a compound that affects cell proliferation by measuring the amount of HSPG in cells exposed to the compound. Applicant further submits that the `613 patent does not provide motivation, either expressly or implicitly, to modify the `613 or combine it with Paka et al reference or abstract.

However, given that HSPGs have the ability to inhibit SMC proliferation (see Paka article, page 36403, 2nd col., 2nd ¶), and the that glypican (HSPG member) plays a role in regulating cellular proliferation (the `613 patent), it would have been obvious to one of ordinary skill in the art at the time the invention was made to measure the amount of glypican instead of perlecan.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

March 6, 2006

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600

Maher M. Haddad

MAHER M. HADDAD
PATENT EXAMINER